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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/886,964	06/21/2001	Ya Fang Liu	YFLU-P02-001	6742

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EXAMINER	
WEBER, JON P	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 04/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/886,964	LIU, YA FANG	
	Examiner	Art Unit	
	Jon P Weber, Ph.D.	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36,39,40,43 and 44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36,39,40,43 and 44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission of response with exhibits filed 01 April 2004 has been entered.

Claims 36, 39-40 and 43-44 have been presented for examination.

Claim Rejections - 35 USC § 112

Claims 36, 39, 40, 43 and 44 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is argued that the use of enzyme inhibitors to treat disease is well established in the art as evidenced by Bjelaković et al. (2002). It is argued the Dyker et al. provides evidence of treatment of a degenerative neurological disease with an enzyme inhibitor. It is urged on the basis of these references that the use of enzyme inhibitors to treat degenerative neurological disorders was a matter of routine experimentation for a person of ordinary skill in the art. It is urged that a novel pathway for ameliorating cell death is provided.

The general discussion in Bjelaković et al. (2002) has no clear relevance to the treatment of the specific disease, Parkinson's, claimed herein. The treatment of any disease is not being

challenged. What is being challenged is the specific asserted treatment for Parkinson's disease for which no known treatment exists.

Dyker et al. is directed to the use of perindopril, an ACE inhibitor that impacts the cardiovascular system. Dyker et al are treating stroke. As indicated in Miller et al. (US 6,060,247), stroke is an acute neurological disorder of the brain, not a degenerative neurological disorder. Stroke is the neurological equivalent of a coronary. Hence, Dyker et al. is not relevant to the treatment of degenerative neurological disorders that are thought to progress by undesired apoptosis.

Given the lack of relevance of Bjelaković et al. (2002) and Dyker et al., the conclusion that it was known in the art to treat degenerative neurological disorders is unfounded. Similarly, the conclusion that it is routine experimentation is unfounded. Whether the proposed novel pathway for apoptosis is borne out is speculation based on the instant disclosure.

It is argued that when one considers all the Wands factors as a whole, the instant disclosure meets the requirements. It is asserted that the art is predictable contrary to the position in the Office action. It is asserted that one can reliably predict that an inhibitor of MLK will inhibit neuronal cell death in a neurodegenerative disease. It is urged that animal models for Parkinson's disease were known in the art at the time of filing of the instant application (the relevant date is the priority date of 14 May 1998). A listing from NINDS was provided in evidence. It is asserted that the mechanism involving MLK is reasonable and that sufficient guidance and adequate examples are provided.

The use of animal models is not as straightforward as asserted. Two reviews of these models published long after the relevant date of state of the art are Betarbet et al. (2002) and

Shimohama et al. (2003). Particular attention is given to Table 1 in Betarbet et al., which provides a critical assessment of the advantages and drawbacks of each of these models. The relevance of any of these models to the particular "novel pathway" suggested herein has not been established by argument or disclosure. Betarbet et al. state that the relevance of the acute models to the pathogenesis of Parkinson's is uncertain. Accordingly, the availability of relevant model systems with which to practice the testing is not established. The argument with respect to predictability cannot be given much weight. The use of uncertain animal models to test unknown compounds and assert that the resulting compounds will actually treat Parkinson's successfully is even less predictable. The validity of the proposed model has not been established by evidence. There is only the instant circumstantial evidence of a covariance. The disclosure has not provided guidance on the selection of compounds that not only inhibit these enzymes but that can successfully treat Parkinson's disease. As stated in Brenner v Manson, "A patent is not a hunting license." The standard under 112, first paragraph is not "make and test." There must be specific guidance, not general as to the nature and manner of compounds that will be used in the desired therapy. Contrary to the assertion in the response, it would take a considerable amount of experimentation to find a useful product. One would have to establish the relevance of a particular animal model to the proposed pathway. One would have to screen for compound that block the proposed pathway. One would have to screen from among those inhibitor compounds, those that actually act on the animal model in the desired manner. Finally, one would have to have a reasonable expectation that the studies with the animal model would extrapolate to the human disease. None of these elements had been done at the time the invention was made. The combination of these does involve undue experimentation because there clearly is an inventive

contribution at several of these steps. While the level of skill in the art is high, the level of unpredictability and the necessity to provide considerable inventive contribution is even higher still.

Applicant's arguments filed 01 April 2004 have been fully considered but they are not persuasive. The rejection under 35 U.S.C. 112, first paragraph is adhered to for the reasons of record and the additional reasons above.

Claim Rejections - 35 USC § 103

Claims 36, 39, 40, 43 and 44 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Miller et al. (US 6,060,247).

It is argued that a *prima facie* case of obviousness has not been met because all that has been provided is obvious to try. It is urged that the listing of MLK adenovirus construct at column 29, lines 53-54 fails to provide a reasonable expectation of success and does not explain why one would select MLK out of this list to treat specific neurodegenerative diseases. It is urged that without the instant disclosure's linkage between apoptosis, Parkinson's, and MLK, one would not have selected that particular adenovirus construct. It is urged that Parkinson's is only mentioned in the background. Accordingly it is concluded that motivation has not be established.

Parkinson's disease is established in the background to be a neurodegenerative disease resulting from apoptosis (column 1, lines 19-27). The mechanisms leading to the apoptosis are what are not understood. A specific linkage to MLK and Parkinson's was not established. Nevertheless, a method of screening for suitable compounds to treat neurodegenerative disorders

using adenovirus constructs is presented. It is exemplified with a specific construct. However, Miller et al. clearly state, "The following groups of adenovirus constructs can be used according to the methods of the invention" at column 29, lines 43-45. This is a clear suggestion providing ample motivation to select any of the listed constructs with a reasonable likelihood of success. A reason to select the particular MLK construct out of the list is not necessary when Miller et al consider all of the constructs functional equivalents.

Applicant's arguments filed 01 April 2004 have been fully considered but they are not persuasive. The rejection under 35 U.S.C. 103 is adhered to for the reasons of record and the additional reasons above.

No claims are allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon P Weber, Ph.D. whose telephone number is 571-272-0925. The examiner can normally be reached on daily, off 1st Fri, 9/5/4.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon P Weber, Ph.D.
Primary Examiner
Art Unit 1651

JPW
28 April 2004